RECEIVED
JAN 27 2004
TECH CENTER 1600/2900

UNITED STATES PATENT AND TRADEMARK OFFICE

I, Charles Edward SITCH BA,

Deputy Managing Director of RWS Group plc UK Translation Division, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That the translator responsible for the attached translation is well acquainted with the German and English languages.

3. That the attached is, to the best of RWS Group plc knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 30 May 2001 under the number 101 26 501.8 and the official certificate attached hereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group plc

The 2nd day of December 2003

**FEDERAL REPUBLIC OF GERMANY**

**[Eagle crest]**

**Priority Certificate**

**for the filing of a Patent Application**

**File Reference:** 101 26 501.8

**Filing date:** 30 May 2001

**Applicant/Proprietor:** Aventis Pharma Deutschland GmbH,
Frankfurt am Main/DE

**Title:** Preparation for the removal of abnormal keratinous material

**IPC:** A 61 K 31/17

**The attached documents are a correct and accurate reproduction of the original submission for this Application.**

Munich, 16 January 2002

**German Patent and Trademark Office**

**The President**

pp

[signature]

Nietiedt

[Seal of the German Patent and Trademark Office]

Description

Preparation for the removal of abnormal keratinous material

The present invention relates to a preparation comprising urea, a hydrophilic film-forming agent and water or an alcohol/water mixture and its use for the removal of abnormal keratinous material, as is to be observed, for example, in onychomycoses, psoriasis of the nail or warts. With respect to the abnormal keratinous material, histologically hyperparakeratosis is discernible, which shows itself in an abnormally changed layer structure of the skin or of the nail. Moreover, by means of this invention the physiological barrier function, for example, of brittle nails can be regenerated by hydration.

Urea has been used in dermatological practice for decades. Creams or lotions are known. Urea changes the structure and the properties of the keratin of the horny layer and of the nails. It has a hygroscopic action in the horny layer depending on the carrier, and an antiproliferative action on the epidermis. Urea cleaves disulfide bonds and hydrogen bonds. By means of this, the dead keratinized material is loosened and can then be mechanically detached.

For the detachment or dissolution of changed, in particularly fungally infested, nails, in Germany there is a cream containing 20% urea (Onychomal®) and an ointment, which apart from 40% urea also contains the antimycotic Bifonazol® (1%) and is marketed in a joint pack together with waterproof plasters, an aid for squeezing out and a nail scraper (Mycospor® nail set). These preparations have been commercially available for over 10 years (Bang DS, Lee YD, Whang KK, Lee SN). Therapeutic trial of ointment base including urea and antifungal agent as the treatment of onychomycosis. Ann Dermatol 1991; 3: 32-6; Hay RJ, Roberts DT, Doherty VR, Richardson MD, Midgley G. The topical treatment of onychomycosis using a new combined urea/imidazole preparation. Clin Exper Dermatol 1988; 13: 164-167).

In addition, a nail varnish is also known, comprising a hydrophobic film-forming agent, an antimycotic and urea, which is employed for the treatment of onychomycoses (US 5,346,692).

Disadvantages in the use of the known cream preparations are frequently occurring maceration and inflammatory changes of the surrounding skin. Moreover, the semisolid preparations necessitate a dressing on the affected sites in order to prevent wiping off, and protection of the surrounding tissue, e.g. by covering with zinc paste. Decisive success was denied to the known treatment methods, since the treatment – for example because of the plasters on the toes and fingers which are bothersome and appear unsightly and the measures which are necessary daily – is frequently not seen through by the patients for cosmetic reasons and for reasons of time. The time needed for the hitherto customary process is comparatively high, and the acceptance is limited or the compliance is rapidly exhausted, if, for example, more than 3 to 5 nails have to be treated.

For the detachment of indurated areas of skin such as in the case of warts, salicylic acid preparations are customarily used in the form of semisolid preparations such as salicyl petroleum jelly (approximately 20% – 60%) or plasters (Guttaplast® ). Here too, the disadvantages of the semisolid preparations apply analogously.

The invention aims, by the provision of a preparation comprising a hydrophilic film-forming agent, urea, water and/or an alcohol/water mixture, to improve the disadvantages mentioned.

The preparation according to the invention is an aqueous or aqueous-alcoholic solution, in which the hydrophilic film-forming agent and urea are dissolved or optionally suspended. A solution is advantageous. After application to the abnormal keratinous material such as warts or fingernails, the preparation rapidly forms an adherent film which is resistant to wiping and rubbing off, from which the urea penetrates into the abnormal keratin and assists its detachment. Additional covering with plasters, the application of a special protective film for the areas of skin surrounding the target site and daily bathing are not necessary. The preparation according to the invention prevents undesired locally occurring precipitation reactions of the urea on the keratinous material to be treated, which lead to unsightly changes or to possible impairments of the local bioavailability. The preparation according to the invention on the contrary makes possible a uniform distribution of the urea on the keratinous material by means of the composition according to the invention and its pharmaceutical properties.

Unlike the products known in the prior art, the invention therefore offers markedly improved drug targeting such as focused application to the target organ or target site with decreased risk for the adjacent tissue, and an improved user-friendliness (handling) in the application of the preparation according to the invention.

The preparation according to the invention therefore provides a formulation comprising

a) urea in an amount from 40 to 70 percent by weight, based on the nonvolatile constituents of the preparations,

b) a hydrophilic film-forming agent and

c) water or an alcohol-water mixture.

The preparation can in addition contain further volatile and nonvolatile constituents as long as the amount of urea, based on the nonvolatile constituents of the preparations, is not exceeded or fallen below.

The amounts of urea are in each case based on the nonvolatile constituents of the preparation according to the invention and are preferably from 41 percent by weight to 69 percent by weight, in particular from 45% by weight to 65% by weight, particularly preferably from 46% by weight to 63% by weight, furthermore preferably from 55% by weight to 63% by weight.

Possible hydrophilic film-forming agents are, for example, acrylic/methacrylic acid ester copolymers, polyvinylpyrrolidones, polyvinyl alcohols, vinyl acetate/vinylpyrrolidone copolymers, vinyl acetate/ crotonic acid copolymers, methyl vinyl ether/maleic acid copolymers, polyesters, polyester amides, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose und hydroxypropylmethylcellulose or a mixture of the film-forming agents mentioned. Polyvinylpyrrolidones are particularly suitable.

The hydrophilic film-forming agents are employed in amounts from 30% by weight to 60% by weight, based on the nonvolatile constituents. The amount of the hydrophilic film-forming agents depends on the amount of urea and makes up, depending on the amount of urea and further optionally present nonvolatile excipients, to 100%.

In the aqueous-alcoholic solutions, alcohols, for example ($C_1$-$C_6$)-alcohols such as methanol, ethanol, propanol, isopropanol (2-propanol), butanol, pentanol hexanol or mixtures thereof, are employed. Ethanol, n-propanol or 2-propanol are preferably employed. In the aqueous-alcoholic solutions, the ratio of alcohol to water is from 9 : 1 to 1 : 9; 2 parts of alcohols to 3 parts of water are preferred.

Suitable further excipients are plasticizers such as glycerol triacetate or 1,2-propylene glycol, and agents for adjusting the pH of the preparations, for example lactic acid or citric acid. Preferably, lactic acid is employed in an amount from 0.5% by weight to 5% by weight, based on the weight of the entire preparation.

The preparations according to the invention can furthermore contain additives which are customary in cosmetics, such as plasticizers based on phthalate, glyceryl triacetate or camphor, colorants or color pigments, pearl luster agents, sulfonamide resins, sedimentation-delaying agents, silicates, odoriferous substances, wetting agents such as sodium dioctylsulfosuccinate, lanolin derivatives, sunscreen agents such as 2-hydroxy-4-methoxybenzophenone or antibacterially active substances. Colored or pigmented nail varnishes, for example, have the advantage that the preparation according to the invention can be tailored to the perception of beauty of the patient and the nail changes existing in the meantime are not immediately visible to third parties.

The preparation according to the invention is prepared by introduction of urea and hydrophilic film-forming agent into water/alcohol and subsequent mixing. Preferably, aqueous-alcoholic solutions are prepared in which the urea is present in dissolved form in an amount from 15% to 35%, based on the weight of the entire solution. The amount of hydrophilic film-forming agent is then from approximately 15% to approximately 35%, in each case based on the weight of the entire solution. The amount of the hydrophilic film-forming agents depends on the amount of urea and makes up, depending on the amount of urea and further nonvolatile excipients which are optionally present, to in each case 100%. The proportion of water or of the aqueous-alcoholic mixture is from 30% to 60%, preferably from 35% to 55%, in each case based on the weight of the entire solution.

The preparation according to the invention is preferably applied as a solution to the keratinous materials to be treated. It dries rapidly and rapidly forms an adherent film

which is resistant to wiping and rubbing off. The solution is applied, for example, with a brush.

The invention further relates to use of the preparation according to the invention for the detachment of abnormal keratinous material.

The term "abnormal keratinous material " is understood as meaning keratinous material in humans and animals such as warts, calluses, hard skin or toe- und fingernails, which has been changed by fungal attack or psoriatic disease. With respect to the abnormal keratinous material, histologically hyperparakeratosis is discernible, which is seen in an abnormally modified layer structure of the skin or the nail.

The invention also relates to the use of a preparation comprising

a) urea in an amount from 30 percent by weight to 90 percent by weight, based on the nonvolatile constituents of the preparations,

b) a hydrophilic film-forming agent and

c) water or an alcohol-water mixture

for the production of a pharmaceutical for the treatment and detachment of abnormal keratinous material.

The amounts of urea are in each case based on the nonvolatile constituents of the use according to the invention and are preferably from 35 to 85 percent by weight, in particular from 39% by weight to 83% by weight, particularly preferably from 46% by weight to 63% by weight, further preferably from 55% by weight to 63% by weight

The hydrophilic film-forming agents are employed in amounts from 10 percent by weight to 70 percent by weight, based on the nonvolatile constituents. The amount of the hydrophilic film-forming agents depends on the amount of urea and makes up, depending on the amount of urea and further optionally present nonvolatile excipients, to 100%. Mixtures of approximately 25% to 35% of urea with 15% to 20% of hydrophilic film-forming agent are advantageous, since they have a shorter drying time than formulations having a higher or lower content of hydrophilic film-forming agent.

In the uses according to the invention, the same alcohols can be employed as in the preparation according to the invention. The amount of water and/or alcohol is analogous to the preparation according to the invention. The hydrophilic film-forming agents which can be employed correspond to the film-forming agents mentioned for the preparation according to the invention. Furthermore, in the use according to the invention, even further excipients or additives such as in the preparation according to the invention can be employed.

The invention also relates to the use of an aqueous solution comprising urea in an amount from 15% to 35%, preferably from 25% to 33%, based on the weight of the entire solution, and a hydrophilic film-forming agent in an amount from approximately 15% to approximately 35%, preferably from 17% to 25%, in each case based on the weight of the entire solution,
for the production of a pharmaceutical for the treatment of abnormal keratinous material.

The abnormal keratinous material is detached by application of the preparation and an appropriately long action of the dried preparation or the keratinous material to be treated and subsequent mechanical removal of the abnormal keratinous material.

The invention further relates to the use of the preparation according to the invention for the hydration of brittle toe- or fingernails.

The present invention is explained in greater detail by means of the following examples, but not restricted to these. If not noted otherwise, the quantitative data are based on the weight.

Example 1

A preparation according to the invention has the following composition:

| | |
|---|---|
| Urea | 30% |
| Polyvinylpyrrolidone (molecular weight approximately 11 500) | 20% |
| Demineralized water | 50% |

Example 2

A preparation according to the invention has the following composition:

| | |
|---|---|
| Urea | 30% |
| Polyvinylpyrrolidone (molecular weight approximately 11 500) | 20% |
| Ethanol | 20% |
| Demineralized water | 30% |

Example 3

A preparation according to the invention has the following composition:

| | |
|---|---|
| Urea | 30% |
| Polyvinylpyrrolidone (molecular weight approximately 11 500) | 20% |
| Propan-2-ol | 20% |
| Lactic acid | 1% |
| Demineralized water | 29% |

Example 4

A preparation according to the invention has the following composition:

| | |
|---|---|
| Urea | 30% |
| Polyvinylpyrrolidone (molecular weight approximately 11 500) | 20%. |
| Lactic acid | 1% |
| Demineralized water | 49% |

Example 5

A preparation according to the invention has the following composition:

| | |
|---|---|
| Urea | 30% |
| Polyvinylpyrrolidone (molecular weight approximately 15 000) | 20% |
| Propan-2-ol | 20% |
| Demineralized water | 30% |

Example 6

A preparation according to the invention has the following composition:

| | |
|---|---|
| Urea | 30% |
| Polyvinylpyrrolidone (molecular weight approximately 11 500) | 20% |
| Cremophor EL | 1% |
| Lactic acid | 1% |
| Demineralized water | 48% |

Example 7

Activity testing

2 affected patients were treated on the toenails with the preparation as in Example 3. The preparation according to the invention as in Example 3 was applied once daily to the affected nails with a brush before going to bed. The urea-containing film which formed after the application to the nails was wipe-resistant and waterproof. Special protection of the skin areas surrounding the nails and the application of plaster dressings were therefore not necessary. On account of the high water content of the preparations, the affected toenails were not additionally bathed.

Result:

After treatment for approximately 6 days, one of the patients removed the affected areas of the nail and the subungual tissue debris easily with a scraper. The severe nail

brittleness had disappeared and the severe hyperkeratosis had improved to a medium degree of severity.

After treatment for approximately 6 weeks, the second patient showed that his severe nail brittleness had disappeared and the severe hyperkeratosis was no longer present.

Both patients showed a good treatment result. The tolerability of the preparation according to the invention was very good. Both patients were very satisfied with the handleability on application of the preparation.

Patent claims:

AVE D-2001/A027

1. A preparation which contains
   a) urea in an amount from 40 percent by weight to 70 percent by weight, based on the nonvolatile constituents of the preparation,
   b) a hydrophilic film-forming agent and
   c) water or an alcohol-water mixture.

2. The preparation as claimed in claim 1, wherein urea is present in an amount from 41 percent by weight to 69 percent by weight, and/or the hydrophilic film-forming agent is present in an amount from 29% by weight to 59% by weight, in each case based on the nonvolatile constituents of the preparation.

3. The preparation as claimed in claim 2, wherein urea is present in an amount from 45% by weight to 65% by weight, preferably from 46% by weight to 63% by weight, in each case based on the nonvolatile constituents of the preparation.

4. The preparation as claimed in claim 3, wherein urea is present in an amount from 55% by weight to 63% by weight, in each case based on the nonvolatile constituents of the preparation.

5. The preparation as claimed in one or more of claims 1 to 4, wherein the hydrophilic film-forming agent employed is a compound from the group consisting of acrylic/methacrylic acid ester copolymers, polyvinylpyrrolidones, polyvinyl alcohols, vinyl acetate/vinylpyrrolidone copolymers, vinyl acetate/crotonic acid copolymers, methyl vinyl ether/maleic acid copolymers, polyesters, polyester amides, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose or a mixture thereof.

6. The preparation as claimed in claim 5, wherein polyvinylpyrrolidones are employed as the hydrophilic film-forming agent.

7. The preparation as claimed in one or more of claims 1 to 6, wherein an alcohol from the group consisting of methanol, ethanol, propanol, isopropanol, butanol,

pentanol und hexanol or a mixture thereof is employed in the aqueous-alcoholic solution.

8. The preparation as claimed in claim 7, wherein ethanol, n-propanol or isopropanol is employed as the alcohol.

9. The preparation as claimed in one or more of claims 1 to 8, wherein the ratio of alcohol to water is from 9 : 1 to 1 : 9; preferably 2 parts of alcohol to 3 parts of water are present.

10. The preparation as claimed in one or more of claims 1 to 9, wherein lactic acid is employed in an amount from 0.5% by weight to 5% by weight, based on the weight of the entire preparation.

11. The use of the preparation as claimed in one or more of claims 1 to 10, for the detachment of abnormal keratinous material.

12. The use as claimed in claim 11, wherein the abnormal keratinous material from the group consisting of warts, calluses, hard skin or toe- and fingernails, where the toe- or fingernails have been changed by fungal attack or psoriatic disease, is detached.

13. The use of a preparation comprising

a) urea in an amount from 30 percent by weight to 90 percent by weight, based on the nonvolatile constituents of the preparations,

b) a hydrophilic film-forming agent and

c) water or an alcohol-water mixture

for the production of a pharmaceutical for the treatment or detachment of abnormal keratinous material.

14. The use as claimed in claim 13, wherein urea is present in an amount from 35 percent by weight to 85 percent by weight and/or the hydrophilic film-forming agent is present in an amount from 15% by weight to 65% by weight, in each case based on the nonvolatile constituents of the preparation.

15. The use as claimed in claim 14, wherein urea is present in an amount from 39% by weight to 83% by weight, preferably from 46% by weight to 63% by weight, in each case based on the nonvolatile constituents of the preparation.

16. The use as claimed in claim 15, wherein urea is present in an amount from 55% by weight to 63% by weight, in each case based on the nonvolatile constituents of the preparation.

17. The use as claimed in claim 13, wherein urea is present in an amount from 25 percent by weight to 35 percent by weight and the hydrophilic film-forming agent is present in an amount from 15% by weight to 20% by weight, in each case based on the total weight of the preparation.

18. The use as claimed in one or more of claims 13 to 17, wherein the abnormal keratinous material from the group consisting of warts, calluses, hard skin or toe- and fingernails, where the toe- or fingernails have been changed by fungal attack or psoriatic disease, is detached.

19. The use of an aqueous solution comprising urea in an amount from 15% to 35%, preferably from 25% to 33%, and a hydrophilic film-forming agent in an amount from approximately 15% to approximately 35%, preferably from 17% to 25%, in each case based on the weight of the entire solution,
for the production of a pharmaceutical for the detachment of abnormal keratinous material.

20. The use of the preparation as claimed in one or more of claims 1 to 10, for the hydration of brittle toe- or fingernails.

Abstract: AVE D-2001/A027

Preparation for the removal of abnormal keratinous material

A preparation comprising urea, a hydrophilic film-forming agent, water and/or a water-alcohol mixture is suitable for the removal of abnormal keratinous material.